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| (71) Applicant: F. HOFFMANN-LA ROCHE AG [CH/CH]; Grenzacherstrasse 124, CH-4070 Basle (CH). | | Published <i>With international search report.</i> |
| (72) Inventor: MASCIADRI, Raffaello; Klybeckstrasse 228, CH-4057 Basle (CH). | | |
| (74) Agent: MAHE, Jean; Grenzacherstrasse 124, CH-4070 Basle (CH). | | |
| (54) Title: DIAMINOPYRIMIDINES, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND THEIR USE AS ANTIBACTERIAL | | |
| (57) Abstract | | |
| Diaminopyrimidines of general formula (I) wherein either R ¹ signifies straight-chain C ₅ -10-alkyl, branched C ₃ -5-alkyl, C ₃ -6-cycloalkyl or C ₃ -5- ω -carboxyalkyl and R ² and R ³ signify C ₁ -5-alkyl; or R ¹ signifies hydrogen, R ² signifies C ₃ -5- ω -carboxyalkyl and R ³ signifies C ₁ -5-alkyl; and their pharmaceutically acceptable acid addition salts have antibiotic properties and can be used in the control or prevention of infectious diseases. | | |
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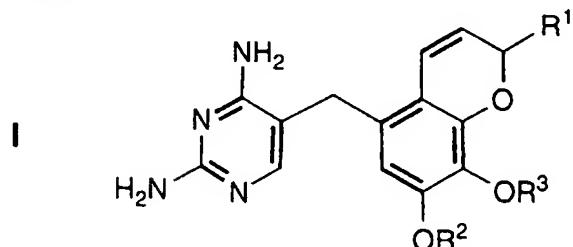
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- 1 -

DIAMINOPYRIMIDINES, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND THEIR USE AS ANTIBACTERIAL

The present invention is concerned with compounds of general formula I



wherein

- 10 either
R¹ signifies straight-chain C₅₋₁₀-alkyl, branched C₃₋₅-alkyl,
C₃₋₆-cycloalkyl or C₃₋₅- ω -carboxyalkyl and R² and R³ signify
C₁₋₅-alkyl;
or
15 R¹ signifies hydrogen, R² signifies C₃₋₅- ω -carboxyalkyl and R³
signifies C₁₋₅-alkyl;
and their pharmaceutically acceptable acid addition salts.

These compounds are novel and have valuable antibiotic properties. They can be used in the control or prevention of infectious diseases. In particular, they exhibit a pronounced antibacterial activity, even against multiresistant, gram-positive strains and against opportunistic pathogens such as e.g. *Pneumocystis carinii*. The compounds can also be administered in combination with known antibacterially active substances and then exhibit synergistic effects. Typical combination partners are e.g. sulphonamides which can be admixed in different proportions with the compounds of formula I or their salts.

- 30 Objects of the present invention are compounds of formula I, their readily hydrolyzable esters and pharmaceutically acceptable salts per se and for use as therapeutically active substances; medicaments based on these substances, optionally in combination with sulphonamides, and their production; the use of

these substances as medicaments and for the production of antibacterially active medicaments; as well as the manufacture of the compounds of formula I and their pharmaceutically acceptable salts and intermediates for their manufacture.

5

The terms C₁₋₅, C₃₋₅ and C₅₋₁₀ denote the number of carbon atoms in the groups in question. Examples of C₁₋₅-alkyl groups are methyl, ethyl, propyl, isopropyl, n-butyl and isomers thereof and n-pentyl and isomers thereof. Cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl are examples of C₃₋₆-cycloalkyl groups. n-Pentyl, n-hexyl and n-heptyl are examples of straight-chain C₅₋₁₀-alkyl groups. Isopropyl, sec.butyl and amyl are examples of branched C₃₋₅-alkyl groups. ω -Carboxypropyl is a preferred C₃₋₅- ω -carboxyalkyl group.

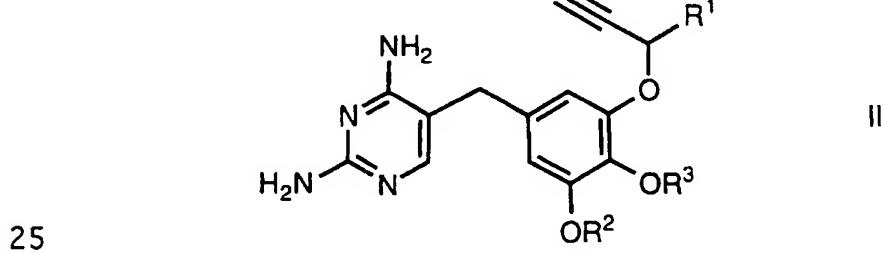
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A preferred group of compounds of formula I comprises those in which R¹ signifies straight-chain C₅₋₁₀-alkyl, branched C₃₋₅-alkyl, C₃₋₆-cycloalkyl or C₃₋₅- ω -carboxyalkyl.

15

The compounds of formula I can be manufactured in accordance with the invention by

- cyclizing a compound of the formula

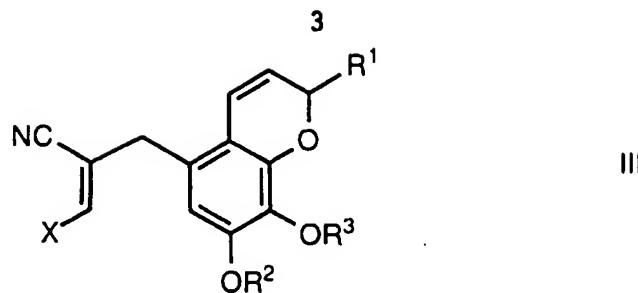


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in which R¹, R² and R³ have the above significance;

or

- reacting a compound of the formula



in which R¹, R² and R³ have the above significance and X represents a leaving group,

5 with guanidine and cleaving off protecting groups present,

and, if desired, converting a thus-obtained compound of formula I into a pharmaceutically usable salt.

10 The cyclization in accordance with process variant a) can be carried out in a manner known per se, e.g. by heating a compound of formula II, conveniently in a high-boiling solvent such as N,N-diethylaniline, polyethylene glycol 400, nitrobenzene, o-dichlorobenzene or diphenyl ether, e.g. to about 180-220°C; or by
 15 treating it with a silver or mercury salt in a chlorinated solvent at about 20-120°C, see in this respect W.K.Anderson and E.J.LaVoie, J. Org. Chem., 38, 3832 (1973), Chem. Reviews 84, 221-223 (1984) and S.M.Daluge, P.M.Skonezny, EP 0051879 (11.11.1981).

20

The reaction in accordance with process variant b) can also be effected in a manner known per se (see e.g. P.S. Manchand et al., J.Org. Chem. 57, 3531-3535 (1992)). Alkoxy such as methoxy, arylamino such as anilino and morpholino are examples of leaving

25 groups X.

The compounds of formula I which form pharmaceutically acceptable acid addition salts with organic and inorganic acids.

Examples of acid addition salts of compounds of formula I are

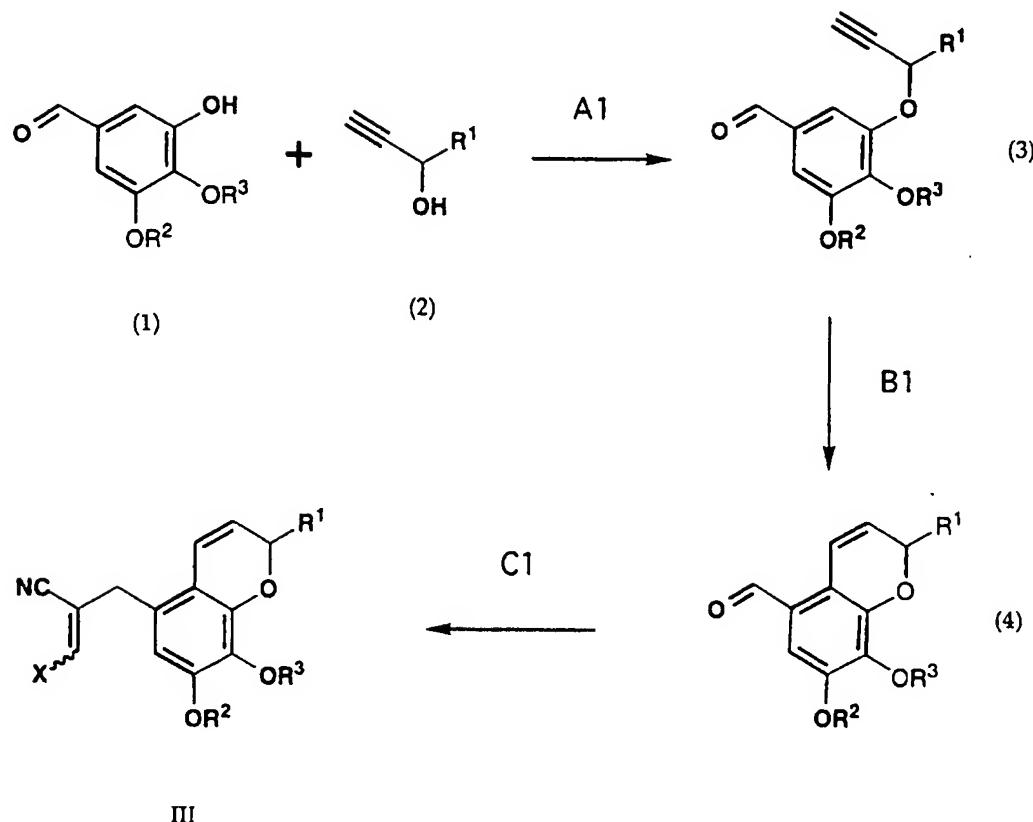
30 salts with mineral acids, for example hydrohalic acids such as hydrochloric acid, hydrogen bromide and hydrogen iodide, sulphuric acid, nitric acid, phosphoric acid and the like, salts with organic sulphonic acids, for example with alkyl- and

arylsulphonic acids such as methanesulphonic acid, p-toluene-sulphonic acid, benzenesulphonic acid and the like, as well as salts with organic carboxylic acids, for example with acetic acid, tartaric acid, maleic acid, citric acid, benzoic acid, salicylic acid, ascorbic acid and the like.

The compounds of formula I which contain a carboxyl group also form pharmaceutically acceptable salts with bases.

Examples of such salts of compounds of formula I are alkali metal salts, for example sodium and potassium salts, ammonium salts, salts with organic bases, for example with amines such as diisopropylamine, benzylamine, dibenzylamine, triethanolamine, triethylamine, N,N-dibenzylethylenediamine, N-methylmorpholine, pyridine, piperazine, N-ethylpiperidine, N-methyl-D-glucamine and procaine, or with amino acids such as arginine and lysine.

The compounds of formulae II and III are novel and are also objects of the invention. They can be prepared according to the following Reaction Schemes in which R¹, R², R³ and X have the above significance.

Reaction Scheme 1

5 Reaction A1

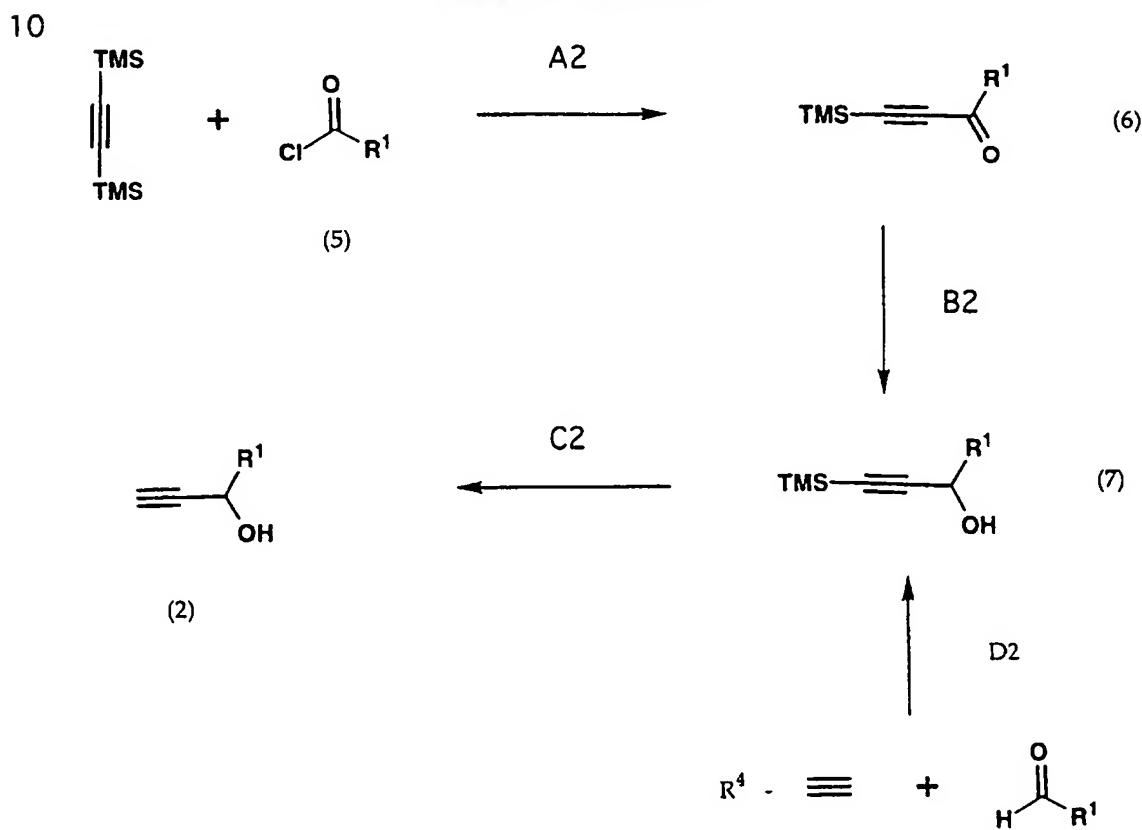
This reaction can be carried out according to methods known per se (see e.g. O. Mitsunobu, *Synthesis* 1981, 1). It is preferably carried out in an inert solvent such as e.g. dichloromethane, tetrahydrofuran or toluene in a temperature range of 10 -10°C to +50°C in the presence of triphenylphosphine and a dialkyl azodicarboxylate. Where the propargyl halide or tosylate corresponding to the alcohol (2) is accessible, a normal alkylation of the phenol group can also be carried out (see reaction D3).

15 Reaction B1

This reaction can also be carried out according to methods known per se in analogy to process variant a) described above for the manufacture of compounds of formula I.

Reaction C1

This reaction can also be carried out according to methods known per se. It is preferably carried out in an inert solvent such as e.g. dimethyl sulphoxide, N,N-dimethylformamide, etc. in a 5 temperature range of 20°C to 100°C in the presence of a strong base such as potassium tert.-butylate or sodium hydride, see e.g. P.S. Manchand et al., J. Org. Chem. 57, 3531-3535 (1992).

Reaction Scheme 2

Reaction A2

This reaction can also be carried out according to methods known per se (see D.R.M. Walton and F.Waugh, J. Organomet. Chem. 15 37, 45 (1972) and K.C.Nicolaou et al, J. Am. Chem. Soc., 106, 3548 (1984)). It is preferably carried out in an inert solvent such as e.g. dichloromethane in a temperature range of -30°C to 0°C in the presence of stoichiometric amounts of aluminium chloride and 20 bis(trimethylsilyl)-acetylene.

Reaction B2

This reaction can also be carried out according to methods known per se (see A.L.Gemal and J.-L.Luche, J. Am. Chem. Soc., 103, 5454 (1981)).

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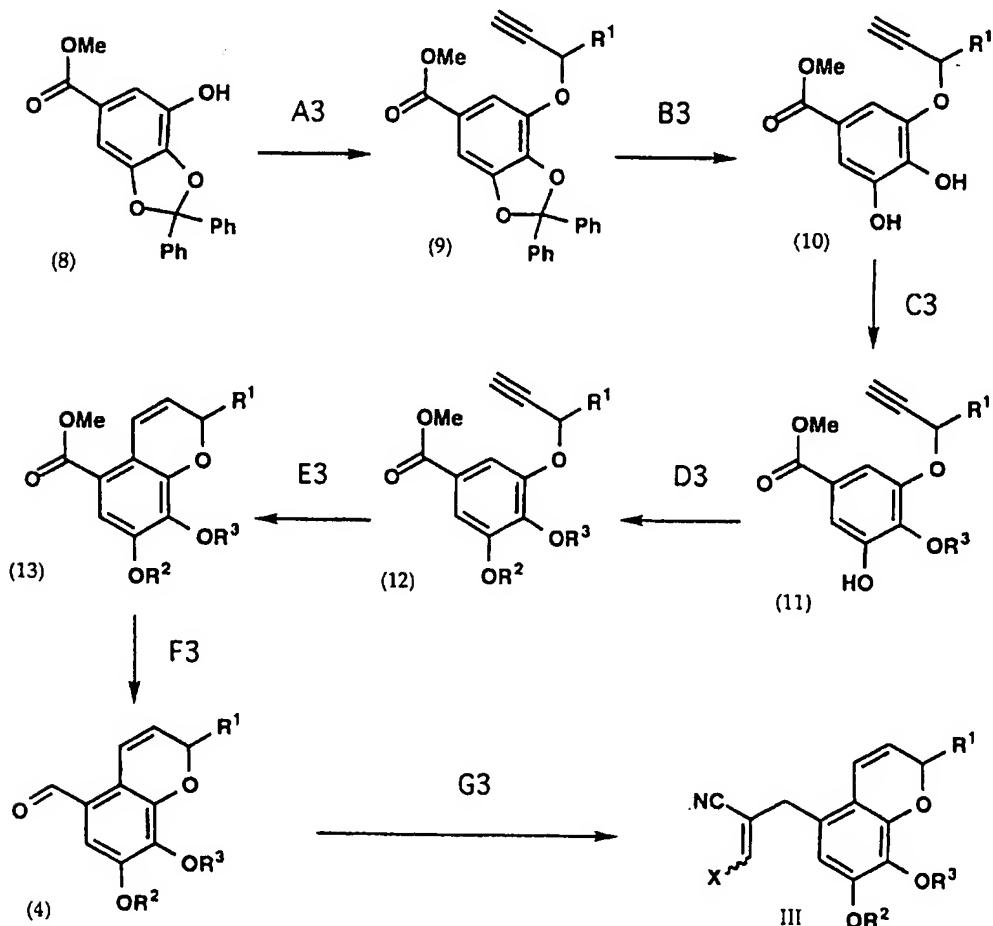
Reaction C2

This reaction can also be carried out according to methods known per se.

10 Reaction D2

This reaction can also be carried out according to methods known per se, see J.A.Katzenellenbogen et al, J. Org. Chem. 54, 2624 (1991) (for R⁴ = tetramethylsilyl) and K.Mori et al., Liebigs Ann. 1991, 529.

15

Reaction Scheme 3

Reaction A3

This reaction is carried out analogously to reaction A1.

5

The starting material (8) is known, see L. Jurd, J. Am. Chem. Soc., 81, 4606 (1959).

Reaction B3

10 This reaction can also be carried out according to methods known per se. Preferably, compound (9) in an inert solvent such as e.g. dichloromethane, tetrahydrofuran or toluene is treated with a protic acid such as hydrochloric acid, sulphuric acid or trifluoroacetic acid in the presence of water in a temperature
15 range of 20°C to 100°C.

Reaction C3

A selective alkylation of the 4-hydroxy group in compound (11) can be accomplished by reaction with an alkyl iodide in the
20 presence of a weak base such as sodium hydrogen carbonate at 0°C to 30°C in an aprotic dipolar solvent such as N,N-dimethyl-formamide.

Reaction D3

25 This reaction can also be carried out according to methods known per se. It can be carried out using an alkyl halide either in an inert solvent such as e.g. dimethyl sulphoxide, N,N-dimethyl-formamide, etc. in a temperature range of 10°C to 50°C in the presence of a strong base such as potassium tert.-butylate or
30 sodium hydride, or in a polar solvent such as acetone, 2-butanone etc. in a temperature range of 50°C to 100°C in the presence of potassium carbonate.

Reaction E3

35 This reaction can also be carried out according to methods known per se analogously to variant a) of the process referred to a) above.

Reaction F3

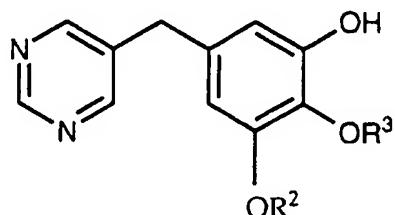
This reaction can be carried out in one step or in two steps according to methods known per se. The one-step method (see R.Kanazawa and T.Tokoroyama, *Synthesis* 1976, 526) is preferably carried out at -30° to -10°C. The two-step method involves a complete reduction to the corresponding alcohol with aluminium hydrides such as DIBALH or REDAL and subsequent re-oxidation to the aldehyde with activated manganese dioxide or by Swern oxidation with dimethyl sulphoxide/oxalyl chloride.

10

Reaction G3

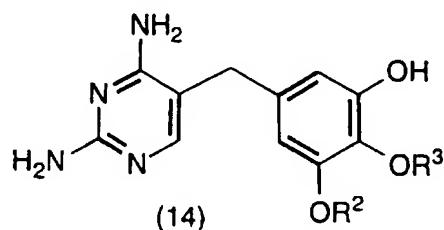
This reaction corresponds to reaction C1.

Compounds of formula II can be prepared from compounds of
15 the formula



and compounds of formula (2) analogously to reaction A1.

20 Compounds of formula II can be prepared from compounds of formulae (2) and (14)



25 in analogy to reaction A1.

The preparation of compounds II and III is, moreover, described in the Examples.

As already mentioned, the compounds of formula I and their pharmaceutically acceptable salts have valuable antibacterial properties. They are active against a large number of pathogenic microorganisms such as e.g. *Staphylococcus aureus*, *Pneumocystis carinii* etc. by virtue of their activity in inhibiting bacterial dihydrofolate reductase (DHFR).

The inhibition of this enzyme was taken as a measurement for the antibacterial activity. It is determined using the method 10 of Baccanari and Joyner (*Biochemistry* 20, 1710 (1981); see also P.G. Hartman et al., *FEB* 242, 157-160 (1988)).

The IC₅₀ values (concentration at which the enzyme is inhibited by 50%) are determined by means of a graph.

15 The following Table contains inhibitory concentrations obtained for representative members of the class of compound defined by formula I and determined in the above test. The IC₅₀ values (μM) against the purified DHFR of the reference strain *S. aureus* ATCC 25923 as well as against the purified DHFR of the multiresistant strain *S. aureus* 157/4696 are given. The third column shows the IC₅₀ values (μM) against the purified DHFR of the opportunistic pathogen *P. carinii*. The inhibition constants of trimethoprim (TMP) are also given as a comparison.

25

| Compound of Example No. | <i>S. aureus</i> ATCC 25923 | <i>S. aureus</i> 157/4696 | <i>P. carinii</i> |
|-------------------------|-----------------------------|---------------------------|-------------------|
| 6 | 0.005 | 0.770 | 0.220 |
| 7 | 0.016 | 0.850 | 2.800 |
| 8 | 0.001 | 1.000 | 1.000 |
| 9 | 0.001 | 0.900 | 3.000 |
| 10 | 0.005 | 0.520 | 0.040 |
| TMP | 0.007 | 2.250 | 5.500 |

The products in accordance with the invention can be used as medicaments, e.g. in the form of pharmaceutical preparations

- for enteral or parenteral administration. For example, the products in accordance with the invention can be administered perorally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions,
- 5 rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The production of the pharmaceutical preparations can be effected in a manner which will be familiar to any person skilled
10 in the art by bringing the substances in accordance with the invention, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, the
15 usual pharmaceutical adjuvants.

Both inorganic and organic carrier materials are suitable as such carrier materials. Thus, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used as
20 carrier materials for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats and semi-solid and liquid polyols (depending on the nature of the active ingredient no carriers are, however, required in the case of soft gelatine
25 capsules). Suitable carrier materials for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar and glucose. Suitable carrier materials for injection solutions are, for example, water, alcohols, polyols, glycerol and vegetable oils. Suitable carrier materials for suppositories are,
30 for example, natural or hardened oils, waxes, fats and semi-liquid or liquid polyols.

The usual preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for
35 varying the osmotic pressure, buffers, masking agents and anti-oxidants come into consideration as pharmaceutical adjuvants.

For parenteral administration the compounds of formula I and, respectively, their salts are preferably provided as lyophilizates or dry powders for dilution with usual carriers such as water or isotonic saline.

5

The compounds of formula I are distinguished by a high antibacterial activity and, respectively, a pronounced synergistic effect in combination with sulphonamides and good tolerance. They inhibit bacterial dihydrofolate reductase and potentiate the 10 antibacterial activity of sulphonamides such as e.g. sulfisoxazole, sulfadimethoxine, sulfamethoxazole, 4-sulphanilamido-5,6-dimethoxy-pyrimidine, 2-sulphanilamido-4,5-dimethyl-pyrimidine or sulfaquinoxaline, sulfadiazine, sulfamonomethoxine, 2-sulphanilamido-4,5-dimethyl-isoxazole and other 15 inhibitors of enzymes which are involved in folic acid biosynthesis, such as e.g. pteridine derivatives.

Oral, rectal and parenteral administration come into consideration in human medicine for such combinations of one or 20 more compounds I in accordance with the invention with sulphonamides. The ratio of compound I to sulphonamide can vary within a wide range; it amounts to e.g. between 1:40 (parts by weight) and 1:1 (parts by weight); preferred ratios are 1:10 to 1:2.

25 Thus, e.g., a tablet can contain 80 mg of a compound I in accordance with the invention and 400 mg of sulfamethoxazole, a tablet for children can contain 20 mg of a compound I in accordance with the invention and 100 mg of sulfamethoxazole; syrup (per 5 ml) can contain 40 mg of compound I and 200 mg of 30 sulfamethoxazole.

A daily dosage of about 0.2 g to about 2 g of a compound of formula I in accordance with the invention comes into consideration for adults.

35

The following Examples illustrate the invention in more detail. Examples 1-4 describe the preparation of starting materials of formulae II and III, while Examples 5-10 describe

the manufacture of the compounds of formula I. The temperatures are given in degrees Celsius.

Example 1

5

Preparation of compounds (2):

- a) 29.3 g of aluminium(III) chloride were suspended in 300 ml of dichloromethane under argon and cooled to -30°C. A solution of 10 44.2 ml of bis(trimethylsilyl)acetylene and 18.3 ml of cyclopropanecarboxylic acid chloride were added at -30°C over 15 min. The reaction mixture was left to warm to -10°C, poured into a vigorously stirred mixture of 250 ml of 3N HCl and 500 g of ice, stirred for a further 10 min. and finally extracted with 15 2 x 750 ml of hexane. The organic phases were washed in succession with in each case 750 ml of saturated NaCl, NaHCO₃ and NaCl. The organic phases were dried and evaporated. Distillation of the crude product at 95°C/14 mbar yielded 1-cyclopropyl-3-trimethylsilyl-prop-2-yn-1-one as a 20 colourless oil.
- b) 37.3 g of Cer(III) chloride heptahydrate were added to a solution of 16.6 g of (RS)-1-cyclopropyl-3-trimethylsilyl-prop-2-yn-1-one in 170 ml of methanol and the mixture was 25 stirred at 20°C until all had dissolved. Then, 1.9 g of sodium borohydride were added cautiously in portions in order to avoid excessive foaming. The resulting white suspension was cooled to 10°C, treated with 50 ml of 1N HCl and then diluted with 150 ml of ice-water. This mixture was extracted with 2 x 400 ml of 30 hexane. The hexane phases were washed with 300 ml of ice-water, dried (Na₂SO₄) and evaporated. Distillation of the crude product at 106°C/14 mbar gave (RS)-1-cyclopropyl-3-trimethylsilyl-prop-2-yn-1-ol as a yellowish oil.
- 35 c) 7.8 g of (RS)-1-cyclopropyl-3-trimethylsilyl-prop-2-yn-1-ol were dissolved in 80 ml of methanol, treated with 0.64 g of potassium carbonate and stirred at 20°C for 3 hrs. Then, the methanol was removed on a rotary evaporator at 200 mbar/40°C.

The residue was taken up in 80 ml of diethyl ether and extracted with 80 ml of ice-water. The crude product was distilled at 14 mbar/60°C (danger of explosion!). (RS)-1-Cyclopropyl-prop-2-yn-1-ol was obtained as a colourless oil.

5

- d) In analogy to Example 1a), from glutaric acid monomethyl-ester chloride there was obtained methyl 5-oxo-7-trimethyl-silanyl-hept-6-ynoate.
- 10 e) In analogy to Example 1b), from methyl 5-oxo-7-trimethyl-silanyl-hept-6-ynoate there was obtained methyl (RS)-5-hydroxy-7-trimethylsilanyl-hept-6-ynoate.
- 15 f) In analogy to Example 1c), from methyl (RS)-5-hydroxy-7-trimethylsilanyl-hept-6-ynoate there was obtained methyl (RS)-5-hydroxy-hept-6-ynoate.

Example 2

20 Preparation of compounds (3):

- a) 7.3 g of 3,4-dimethoxy-5-hydroxybenzaldehyde, 6.9 g of (RS)-1-cyclopropyl-3-trimethylsilanyl-prop-2-yn-1-ol and 10.5 g of triphenylphosphine were dissolved in 60 ml of toluene under argon and cooled to 5°C. A solution of 6.9 ml of diethyl azodicarboxylate in 20 ml of toluene was slowly added dropwise thereto at 5°C over 50 min. The resulting reaction mixture was chromatographed directly on silica gel in toluene. There were obtained 4.2 g of a yellow oil (HPLC 80%). This was dissolved in 40 ml of methanol and stirred at 20°C with 553 mg of potassium carbonate for 3 hrs. Extraction was effected with in each case 2 x 50 ml of ethyl acetate and water. For crystallization, it was dissolved in 10 ml of hot ethyl acetate and then diluted with 20 ml of hexane. There was obtained (RS)-3-(1-cyclopropyl-prop-2-ynyloxy)-4,5-dimethoxy-benzaldehyde as white crystals.
- b) 63.6 g of methyl 3,4-dimethoxy-5-hydroxy-benzoate [E.Späth and H.Röder, Monatsh. für Chemie, 43, 93 (1923)], 38.5 g

- of (RS)-1-cyclopropyl-prop-2-yn-1-ol and 118 g of triphenylphosphine were dissolved in 600 ml of toluene under argon and cooled to 5°C. A solution of 70 ml of diethyl azodicarboxylate in 150 ml of toluene was slowly added dropwise thereto at 5°C over 5 90 min. The mixture was stirred at 5°C for a further 1 hr. and at 20°C for 3 hrs. Then, 300 ml of toluene were distilled off on a rotary evaporator and the suspension obtained was stirred in an ice bath for 30 min. The separated triphenylphosphine oxide was filtered off and the filtrate was evaporated. The resulting oil 10 was chromatographed on silica gel with hexane/ethyl acetate 4:1, then 3:1. Crystallization was effected from diethyl ether and hexane. There was obtained methyl (RS)-3-(1-cyclopropyl-prop-2-ynyloxy)-4,5-dimethoxy-benzoate as white crystals.
- 15 c) In analogy to Example 2a), from methyl (RS)-5-hydroxy-7-trimethylsilanyl-hept-6-yneate there was obtained methyl (RS)-5-(5-formyl-2,3-dimethoxy-phenoxy)-hept-6-yneate.
- d) In analogy to Example 2a), from (RS)-1-octyn-3-ol there 20 was obtained (RS)-3,4-dimethoxy-5-(1-pentyl-prop-2-ynyloxy)-benzaldehyde.
- e) In analogy to Example 2a), from (RS)-4-methyl-1-pentyn-3-ol there was obtained (RS)-3-(1-isopropyl-prop-2-ynyloxy)-4,5-dimethoxy-benzaldehyde.
- f) In analogy to Example 2a), from (RS)-5-methyl-1-hexyn-3-ol there was obtained (RS)-3-(1-isobutyl-prop-2-ynyloxy)-4,5-dimethoxy-benzaldehyde.

30

Example 3

Preparation of compounds (4):

- 35 a) 33.5 g of methyl (RS)-3-(1-cyclopropyl-prop-2-ynyloxy)-4,5-dimethoxy-benzoate were dissolved in 330 ml of N,N-diethyl-aniline, heated to 200°C under argon and stirred at 200°C for a further 5 hrs. The solvent was distilled off at 90°C/1 mbar and

the residue was extracted: 2 x 1.5 l of diethyl ether, 2 x 1.5 l of 1N HCl, 2 x 1.5 l of saturated NaCl. The oil obtained was purified by silica gel chromatography with toluene, then toluene/ethyl acetate 9:1. Crystallization was effected from diethyl ether and hexane. Methyl (RS)-2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-carboxylate was obtained as white crystals.

b1) 2.4 g of (RS)-3-(1-cyclopropyl-prop-2-ynyoxy)-4,5-dimethoxy-benzaldehyde were dissolved in 20 ml of N,N-diethyl-aniline, heated to 200°C under argon and stirred at 200°C for a further 1 hr. The solvent was distilled off at 90°C/1 mbar and the residue was extracted: 2 x 100 ml of diethyl ether, 2 x 100 ml of 1N HCl, 2 x 100 ml of saturated NaCl. The crude product was purified by two-fold silica gel chromatography with dichloromethane and, respectively, ethyl acetate/hexane 5:1. (RS)-2-Cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-carbaldehyde was obtained as a brown oil (HPLC 96%).

b2) A solution of 48 ml of morpholine in 50 ml of toluene was added dropwise over 1 hr. under argon to an ice-cold solution of 143 ml of sodium dihydrido-bis-(2-methoxyethoxy) aluminate (3.5M in toluene) diluted with 200 ml of toluene. The resulting reduction solution was then added dropwise under argon during 1 hr. to a solution, cooled to -35°C, of 46 g of methyl (RS)-2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-carboxylate in 200 ml of toluene and the mixture was stirred at -15°C for a further 4 hrs. The reaction was stopped by the cautious addition of 40 ml of 3N NaOH and the mixture was left to warm. Extraction: 3 x 600 ml of ice-water, 1 x 600 ml of toluene.

30 Chromatography: silica gel, hexane/ethyl acetate 5:1. Crystallization from diethyl ether/ hexane. (RS)-2-Cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-carbaldehyde was obtained as a solid.

35 c) In analogy to Example 3a), from methyl (RS)-5-(5-formyl-2,3-dimethoxy-phenoxy)-hept-6-ynoate there was obtained methyl (RS)-4-(5-formyl-7,8-dimethoxy-2H-1-benzopyran-2-yl)-butyrate.

- d) 1.5 g of methyl (RS)-4-(5-formyl-7,8-dimethoxy-2H-1-benzopyran-2-yl)-butyrate were dissolved in 10 ml of tetrahydrofuran under argon and then treated with 1 ml of 1N NaOH
5 and stirred at 20°C for 1.5 hrs. The reaction mixture was acidified with 9 ml of 1N HCl, saturated with NaCl and extracted with 2 x 20 ml of ethyl acetate. The crude product was chromatographed on silica gel in ethyl acetate and chromatographed from toluene/hexane 1:1. There was obtained (RS)-4-(5-
10 formyl-7,8-dimethoxy-2H-1-benzopyran-2-yl)-butyric acid as white crystals.
- e) In analogy to Example 3a), from (RS)-3,4-dimethoxy-5-(1-pentyl-prop-2-ynyl)-benzaldehyde there was obtained (RS)-
15 7,8-dimethoxy-2-pentyl-2H-1-benzopyran-5-carbaldehyde.
- f) In analogy to Example 3a), from (RS)-3-(1-isopropyl-prop-2-ynyl)-4,5-dimethoxy-benzaldehyde there was obtained (RS)-2-isopropyl-7,8-dimethoxy-2H-1-benzopyran-5-carbaldehyde.
20
- g) In analogy to Example 3a), from (RS)-3-(1-isobutyl-prop-2-ynyl)-4,5-dimethoxy-benzaldehyde there was obtained (RS)-2-isobutyl-7,8-dimethoxy-2H-1-benzopyran-5-carbaldehyde.
25

Example 4

Preparation of compounds of formula III:

- 30 30 g of (RS)-2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-carbaldehyde and 17.5 g of 3-anilinopropionitrile were dissolved in 300 ml of dimethyl sulphoxide under argon, cooled to 10°C and treated portionwise with 13.5 g of potassium tert.-butylate. Subsequently, the mixture was stirred at 10°C for a further 1 hr. and at 20°C for 5 hrs. For the working up, the
35 mixture was poured on to 3 l of ice/water and extracted: 2 x 3 l of ethyl acetate, 2 x 3 l of water. The crude product was purified by silica gel chromatography with hexane/ethyl acetate 5:1 to 2:1 and crystallized from hexane/ethyl acetate. (RS)-3-

Anilino-2-(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-yl-methyl)acrylonitrile was obtained as white crystals, m.p. 140°C.

Example 5

5

1.45 g of guanidine hydrochloride were dissolved in 20 ml of ethanol, stirred with 1.7 g of potassium tert.butylate for 15 min. and then filtered through Dicalite. The filtrate was added to 2 g of (RS)-3-anilino-2-(2-cyclopropyl-7,8-dimethoxy-
10 2H-1-benzopyran-5-yl-methyl)acrylonitrile and the mixture was boiled at reflux for 8 hrs. The product crystallized out spontaneously upon cooling. Recrystallization from 90 ml of ethanol gave (RS)-5-(2-cyclopropyl-7,8-dimethoxy-2H-1-
15 benzopyran-5-yl-methyl)-pyrimidine-2,4-diamine as white crystals, m.p. 229°C.

Example 6

In analogy to Examples 4 and 5, from (RS)-4-(5-formyl-7,8-dimethoxy-2H-1-benzopyran-2-yl)-butyric acid there was obtained (RS)-4-[5-(2,4-diamino-pyrimidin-5-ylmethyl)-7,8-dimethoxy-2H-1-benzopyran-2-yl]-butyric acid, m.p. 124°C.
20

Example 7

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In analogy to Examples 4 and 5, from (RS)-7,8-dimethoxy-2-pentyl-2H-1-benzopyran-5-carbaldehyde there was obtained (RS)-5-(7,8-dimethoxy-2-pentyl-2H-1-benzopyran-5-ylmethyl)-pyrimidine-2,4-diamine, m.p. 188°C.
30

Example 8

In analogy to Examples 4 and 5, from 2-isopropyl-7,8-dimethoxy-2H-1-benzopyran-5-carbaldehyde there was obtained (RS)-5-(2-isopropyl-7,8-dimethoxy-2H-1-benzopyran-5-yl-methyl)-pyrimidine-2,4-diamine, m.p. 223°C.
35

Example 9

- In analogy to Examples 4 and 5, from (RS)-2-isobutyl-7,8-dimethoxy-2H-1-benzopyran-5-carbaldehyde there was obtained
 5 (RS)-5-(2-isobutyl-7,8-dimethoxy-2H-1-benzopyran-5-yl-methyl)-pyrimidine-2,4-diamine, m.p. 214°C.

Example 10

- 10 In analogy to Examples 4 and 5, from tert-butyl 4-(5-formyl-8-methoxy-2H-1-benzopyran-7-yloxy)-butyrate via tert-butyl 4-[5-(2-cyano-3-phenylamino-allyl)-8-methoxy-2H-chromen-7-yloxy]-butyrate there was obtained 4-[5-(2,4-diamino-pyrimidin-5-ylmethyl)-8-methoxy-2H-1-benzopyran-7-yloxy]-butyric acid, m.p. 250°C.
 15

Example ATablets

| | | |
|----|---|-------------|
| 20 | Sulfamethoxazole | 400 mg |
| | Compound of formula I, e.g. 4-[5-(2,4-diamino-pyrimidin-5-ylmethyl)-8-methoxy-2H-1-benzopyran-7-yloxy]-butyric acid | 80 mg |
| 25 | PRIMOJEL (starch derivative) | 6 mg |
| | POVIDONE K30 (polyvinylpyrrolidone) | 8 mg |
| | Magnesium stearate | <u>6 mg</u> |
| | Total weight | 500 mg |

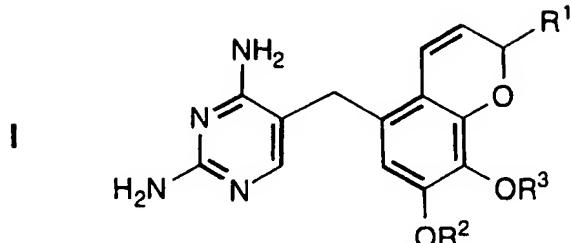
Example B

| | | |
|----|---|-------------|
| 30 | Compound of formula I, e.g. 4-[5-(2,4-diamino-pyrimidin-5-ylmethyl)-8-methoxy-2H-1-benzopyran-7-yloxy]-butyric acid | 100 mg |
| 35 | Corn starch | 15 mg |
| | Talc | 3 mg |
| | Magnesium stearate | <u>2 mg</u> |
| | | 120 mg |

Claims

1. Compounds of general formula I

5



wherein

either

- R¹ signifies straight-chain C₅-10-alkyl, branched C₃-5-alkyl,
10 C₃-6-cycloalkyl or C₃-5- ω -carboxyalkyl and R² and R³ signify
C₁-5-alkyl;
or
R¹ signifies hydrogen, R² signifies C₃-5- ω -carboxyalkyl and R³
signifies C₁-5-alkyl;
- 15 and their pharmaceutically acceptable acid addition salts.

2. Compounds according to claim 1, in which R¹ signifies
straight-chain C₅-10-alkyl, branched C₃-5-alkyl, C₃-6-cyclo-
alkyl or C₃-5- ω -carboxyalkyl.

20

3. The compounds

- 25 (RS)-5-(2-cyclopropyl-7,8-dimethoxy-2H-1-benzopyran-5-yl-methyl)-pyrimidine-2,4-diamine,
- (RS)-4-[5-(2,4-diamino-pyrimidin-5-ylmethyl)-7,8-dimethoxy-2H-1-benzopyran-2-yl]-butyric acid,
- 30 (RS)-5-(7,8-dimethoxy-2-pentyl-2H-1-benzopyran-5-yl-methyl)-pyrimidine-2,4-diamine,

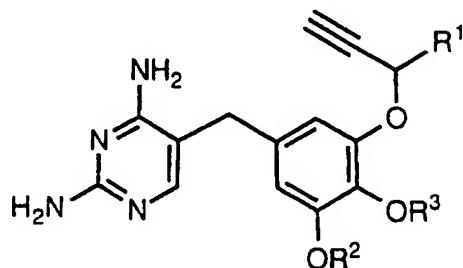
(RS)-5-(2-isopropyl-7,8-dimethoxy-2H-1-benzopyran-5-ylmethyl)-pyrimidine-2,4-diamine and

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4-[5-(2,4-diamino-pyrimidin-5-ylmethyl)-8-methoxy-2H-1-benzopyran-7-yloxy]-butyric acid.

4. Compounds of the formula

5

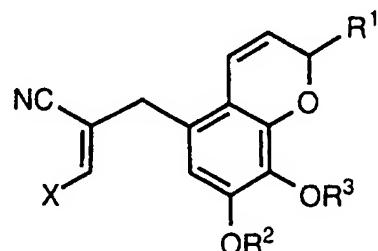


II

wherein R¹, R² and R³ have the significance given in claim 1.

10

5. Compounds of the formula



III

15

in which R¹, R² and R³ have the significance given in claim 1 and X represents a leaving group.

6. Compounds according to any one of claims 1-3 for use as medicaments.

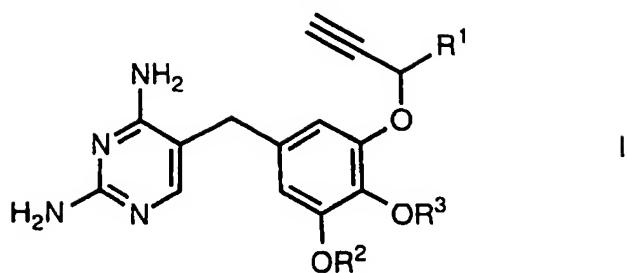
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7. A process for the manufacture of compounds of claims 1-3, which process comprises

a) cyclizing a compound of the formula

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22

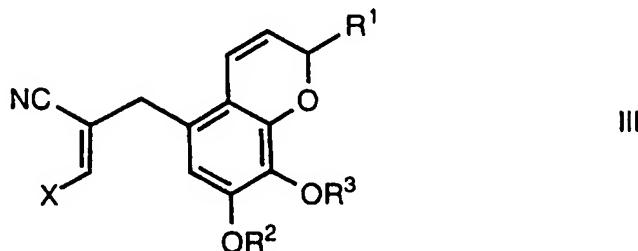


in which R¹, R² and R³ have the above significance;

or

5

- b) reacting a compound of the formula



10 in which R¹, R² and R³ have the above significance and X
represents a leaving group,
with guanidine and cleaving off protecting groups present,

15 and, if desired, converting a thus-obtained compound of formula I
into a pharmaceutically usable salt.

8. A medicament containing a compound according to any
one of claims 1-3 and a therapeutically inert carrier.

20 9. The use of compounds according to any one of claims
1-3 as medicaments, especially in infectious diseases.

10. The use of compounds according to any one of claims
1-3 in the manufacture of antibiotically-active medicaments.

25

11. The invention as hereinbefore described.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 96/05151

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 C07D405/06 A61K31/505 C07D311/64 C07D239/49

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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| X | * see page 21, Formula (XVI) * | 4 |
| X | * see page 18, Formula (X) * | 5 |
| | ----- | |

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Patent family members are listed in annex.

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| 1 Date of the actual completion of the international search | Date of mailing of the international search report |
| 5 February 1997 | 24.02.97 |
| Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016 | Authorized officer Lauro, P |

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